Fig. 1

```
ATGTCCATGA ACTGCTGAGT GGATAAACAG CACGGGATAT CTCTGTCTAA        -96
AGGAATATTA CTACACCAGG AAAAGGACAC ATTCGACAAC AGGAAAGGAG        -46
CCTGTCACAG AAAACCACAG TGTCCTGTGC ATGTGACATT TCGCC              -1

ATG GGA AAC AAC TGT TAC AAC GTG GTG GTC ATT GTG CTG CTG CTA    45
Met Gly Asn Asn Cys Tyr Asn Val Val Val Ile Val Leu Leu Leu

GTG GGC TGT GAG AAG GTG GGA GCC GTG CAG AAC TCC TGT GAT AAC   90
Val Gly Cys Glu Lys Val Gly Ala Val Gln Asn Ser Cys Asp Asn

TGT CAG CCT GGT ACT TTC TGC AGA AAA TAC AAT CCA GTC TGC AAG   135
Cys Gln Pro Gly Thr Phe Cys Arg Lys Tyr Asn Pro Val Cys Lys
                          H4-1BB F1

AGC TGC CCT CCA AGT ACC TTC TCC AGC ATA GGT GGA CAG CCG AAC   180
Ser Cys Pro Pro Ser Thr Phe Ser Ser Ile Gly Gly Gln Pro Asn
                          H4-1BB FII

TGT AAC ATC TGC AGA GTG TGT GCA GGC TAT TTC AGG TTC AAG AAG   225
Cys Asn Ile Cys Arg Val Cys Ala Gly Tyr Phe Arg Phe Lys Lys

TTT TGC TCC TCT ACC CAC AAC GCG GAG TGT GAG TGC ATT GAA GGA   270
Phe Cys Ser Ser Thr His Asn Ala Glu Cys Glu Cys Ile Glu Gly

TTC CAT TGC TTG GGG CCA CAG TGC ACC AGA TGT GAA AAG GAC TGC   315
Phe His Cys Leu Gly Pro Gln Cys Thr Arg Cys Glu Lys Asp Cys

AGG CCT GGC CAG GAG CTA ACG AAG CAG GGT TGC AAA ACC TGT AGC   360
Arg Pro Gly Gln Glu Leu Thr Lys Gln Gly Cys Lys Thr Cys Ser
                                    H4-1BB RI

TTG GGA ACA TTT AAT GAC CAG AAC GGT ACT GGC GTC TGT CGA CCC   405
Leu Gly Thr Phe Asn Asp Gln Asn Gly Thr Gly Val Cys Arg Pro
                H4-1BB RII

TGG ACG AAC TGC TCT CTA GAC GGA AGG TCT GTG CTT AAG ACC GGG   450
Trp Thr Asn Cys Ser Leu Asp Gly Arg Ser Val Leu Lys Thr Gly

ACC ACG GAG AAG GAC GTG GTG TGT GGA CCC CCT GTG GTG AGC TTC   495
Thr Thr Glu Lys Asp Val Val Cys Gly Pro Pro Val Val Ser Phe

TCT CCC AGT ACC ACC ATT TCT GTG ACT CCA GAG GGA GGA CCA GGA   540
Ser Pro Ser Thr Thr Ile Ser Val Thr Pro Glu Gly Gly Pro Gly

GGG CAC TCC TTG CAG GTC CTT ACC TTG TTC CTG GCG CTG ACA TCG   585
Gly His Ser Leu Gln Val Leu Thr Leu Phe Leu Ala Leu Thr Ser

GCT TTG CTG CTG GCC CTG ATC TTC ATT ACT CTC CTG TTC TCT GTG   630
Ala Leu Leu Leu Ala Leu Ile Phe Ile Thr Leu Leu Phe Ser Val

CTC AAA TGG ATC AGG AAA AAA TTC CCC CAC ATA TTC AAG CAA CCA   675
Leu Lys Trp Ile Arg Lys Lys Phe Pro His Ile Phe Lys Gln Pro

TTT AAG AAG ACC ACT GGA GCA GCT CAA GAG GAA GAT GCT TGT AGC   720
Phe Lys Lys Thr Thr Gly Ala Ala Gln Glu Glu Asp Ala Cys Ser
```

Fig.1 (cont'd)

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TGC CGA TGT CCA CAG GAA GAA GAA GGA GGA GGA GGA GGC TAT GAG   765
Cys Arg Cys Pro Gln Glu Glu Glu Gly Gly Gly Gly Gly Tyr Glu
 ●       ●

CTG TGA
Leu ---                                                      771

TGTACTATCC TAGGAGATGT GTGGGCCGAA ACCGAGAAGC ACTAGGACCC       821
CACCATCCTG TGGAACAGCA CAAGCAACCC CACCACCCTG TTCTTACACA       871
TCATCCTAGA TGATGTGTGG GCGCGCACCT CATCCAAGTC TCTTCTAACG       921
CTAACATATT TGTCTTTACC TTTTTTAAAT CTTTTTTTAA ATTTAAATTT       971
TATGTGTGTG AGTGTTTTGC CTGCCTGTAT GCACACGTGT GTGTGTGTGT      1021
GTGTGTGACA CTCCTGATGC CTGAGGAGGT CAGAAGACAA AGGGTTGGTT      1071
CCATAAGAAC TGGAGTTATG GATGGCTGTG AGCCGGNNNG ATAGGTCGGG      1121
ACGGAGACCT GTCTTCTTAT TTTAACGTGA CTGTATATATA AAAAAAAAAT     1171
GATATTTCGG GAATTGTAGA GATTGTCCTG ACACCCTTCT AGTTAATGAT      1221
CTAAGAGGAA TTGTTGATAC GTAGTATACT GTATATGTGT ATGTATATGT      1271
ATATGTATAT ATAAGACTCT TTTACTGTCA AAGTCAACCT AGAGTGTCTG      1321
GTTACCAGGT CAATTTTATT GGACATTTTA CGTCACACAC ACACACACAC      1371
ACACACACAC ACGTTTATAC TACGTACTGT TATCGGTATT CTACGTCATA      1421
TAATGGGATA GGGTAAAAGG AAACCAAAGA GTGAGTGATA TTATTGTGGA      1471
GGTGACAGAC TACCCCTTCT GGGTACGTAG GGACAGACCT CCTTCGGACT      1521
GTCTAAAACT CCCCTTAGAA GTCTCGTCAA GTTCCCGGAC GAAGAGGACA      1571
GAGGAGACAC AGTCCGAAAA GTTATTTTTC CGGCAAATCC TTTCCCTGTT      1621
TCGTGACACT CCACCCCTTG TGGACACTTG AGTGTCATCC TTGCGCCGGA      1671
AGGTCAGGTG GTACCCGTCT GTAGGGGCGG GGAGACAGAG CCGCGGGGGA      1721
GCTACGAGAA TCGACTCACA GGGCGCCCCG GGCTTCGCAA ATGAAACTTT      1771
TTTAATCTCA CAAGTTTCGT CCGGGCTCGG CGGACCTATG GCGTCGATCC      1821
TTATTACCTT ATCCTGGCGC CAAGATAAAA CAACCAAAAG CCTTGACTCC      1871
GGTACTAATT CTCCCTGCCG GCCCCCGTAA GCATAACGCG GCGATCTCCA      1921
CTTTAAGAAC CTGGCCGCGT TCTGCCTGGT CTCGCTTTCG TAAACGGTTC      1971
TTACAAAAGT AATTAGTTCT TGCTTTCAGC CTCCAAGCTT CTGCTAGTCT      2021
ATGGCAGCAT CAAGGCTGGT ATTTGCTACG GCTGACCGCT ACGCCGCCGC      2071
AATAAGGGTA CTGGGCGGCC CGTCGAAGGC CCTTTGGTTT CAGAAACCCA      2121
AGGCCCCCCT CATACCAACG TTTCGACTTT GATTCTTGCC GGTACGTGGT      2171
GGTGGGTGCC TTAGCTCTTT CTCGATAGTT AGAC                       2205
```

Fig. 2a

human homologue of mouse 4-1bb
h4-1bb Length 838

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  1  AATCAGCTTT GCTAGTATCA TACCTGTGCC AGATTTCATC ATGGGAAACA
 51  GCTGTTACAA CATAGTAGCC ACTCTGTTGC TGGTCCTCAA CTTTGAGAGG
101  ACAAGATCAT TGCAGGATCC TTGTAGTAAC TGCCCAGCTG GTACATTCTG
151  TGATAATAAC AGGAATCAGA TTTGCAGTCC CTGTCCTCCA AATAGTTTCT
201  CCAGCGCAGG TGGACAAAGG ACCTGTGACA TATGCAGGCA GTGTAAAGGT
251  GTTTTCAGGA CCAGGAAGGA GTGTTCCTCC ACCAGCAATG CAGAGTGTGA
301  CTGCACTCCA GGGTTTCACT GCCTGGGGGC AGGATGCAGC ATGTGTGAAC
351  AGGATTGTAA ACAAGGTCAA GAACTGACAA AAAAAGGTTG TAAAGACTGT
401  TGCTTTGGGA CATTTAACGA TCAGAAACGT GGCATCTGTC GACCCTGGAC
451  AAACTGTTCT TTGGATGGAA AGTCTGTGCT TGTGAATGGG ACGAAGGAGA
501  GGGACGTGGT CTGTGGACCA TCTCCAGCTG ACCTCTCTCC GGGAGCATCC
551  TCTGTGACCC CGCCTGCCCC TGCGAGAGAG CCAGGACACT CTCCGCAGAT
601  CATCTCCTTC TTTCTTGCGC TGACGTCGAC TGCGTTGCTC TTCCTGCTGT
651  TCTTCCTCAC GCTCCGTTTC TCTGTTGTTA AACGGGGCAG AAAGAAACTC
701  CTGTATATAT TCAAACAACC ATTTATGAGA CCAGTACAAA CTACTCAAGA
751  GGAAGATGGC TGTAGCTGCC GATTTCCAGA AGAAGAAGAA GGAGGATGTG
801  AACTGTGAAA TGGAAGTCAA TAGGGCTGTT GGGACTTT
```
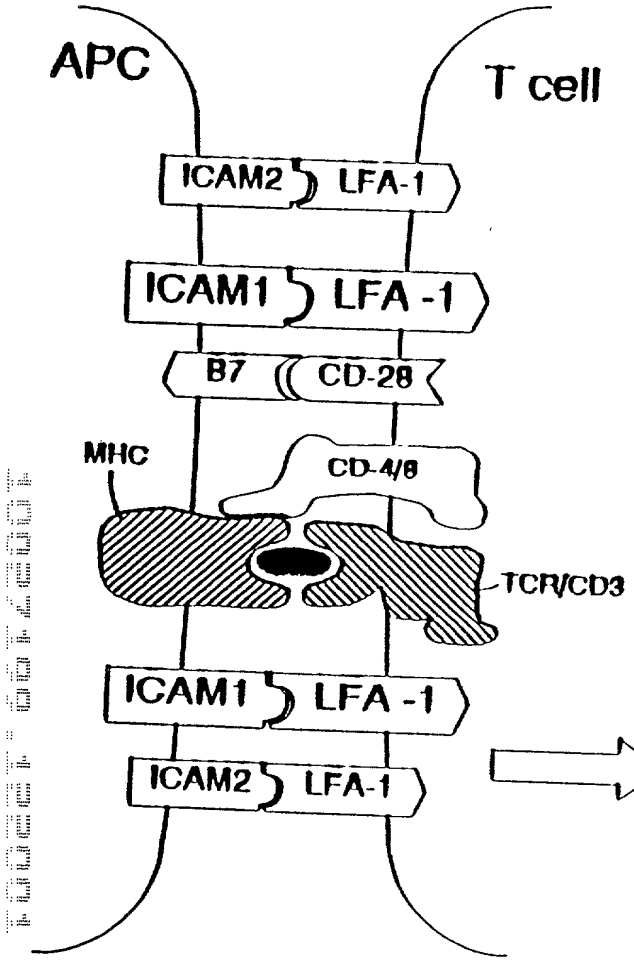
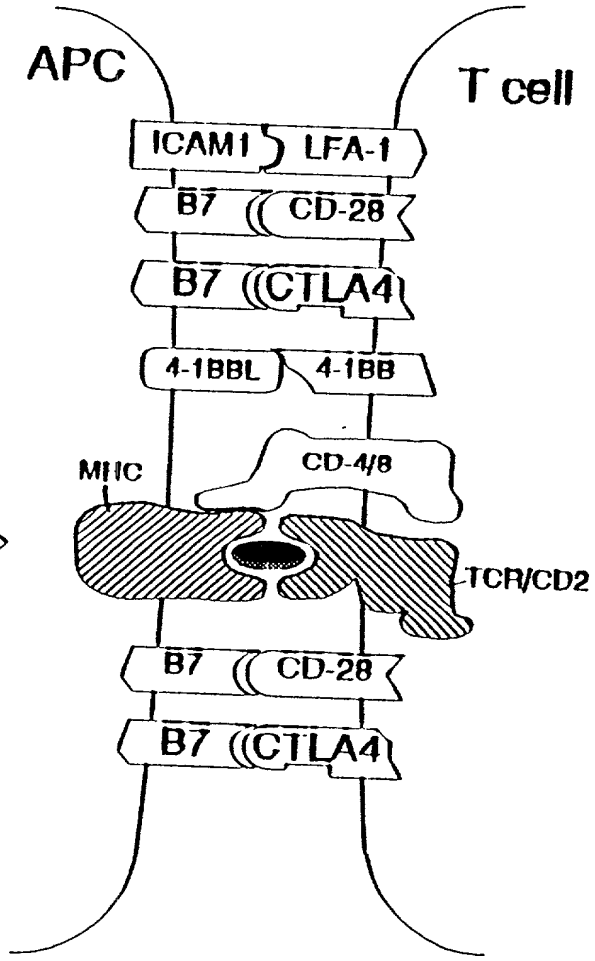

Fig. 2b

```
  1  MGNSCYNIVA TLLLVLNFER TRSLQDPCSN CPAGTFCDNN RNQICSPCPP
 51  NSFSSAGGQR TCDICRQCKG VFRTRKECSS TSNAECDCTP GFHCLGAGCS
101  MCEQDCKQGQ ELTKKGCKDC CFGTFNDQKR GICRPWTNCS LDGKSVLVNG
151  TKERDVVCGP SPADLSPGAS SVTPPAPARE PGHSPQIISF FLALTSTALL
201  FLLFFLTLRF SVVKRGRKKL LYIFKQPFMR PVQTTQEEDG CSCRFPEEEE
251  GGCEL
```



COGNITIVE PHASE
early activation

Fig. 3a



PROLIFERATION
CLONAL EXPANSION
late activation

Fig. 3b

NORMAL T-CELL ACTIVATION PATHWAY

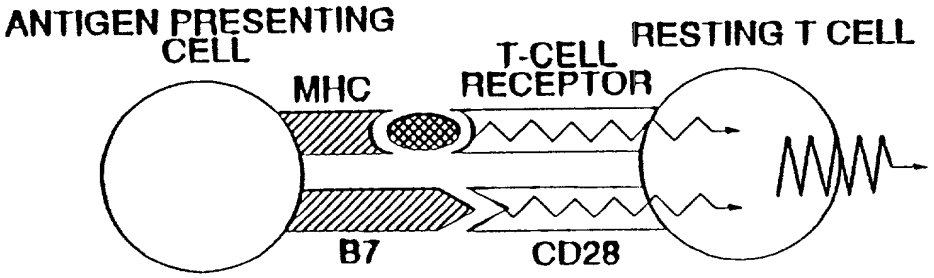


Fig. 4a

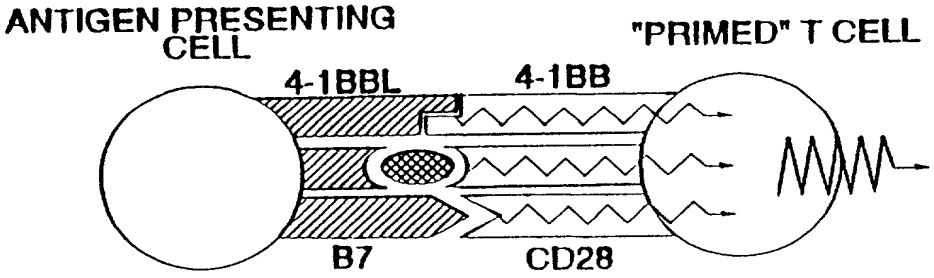


Fig. 4b

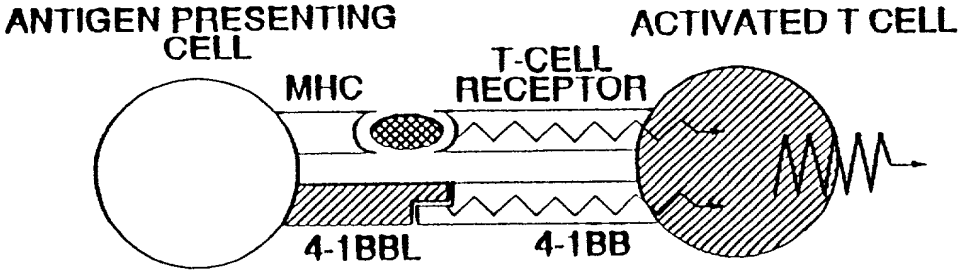


Fig. 4c

BLOCKING STEPS IN T-CELL ACTIVATION PATHWAY

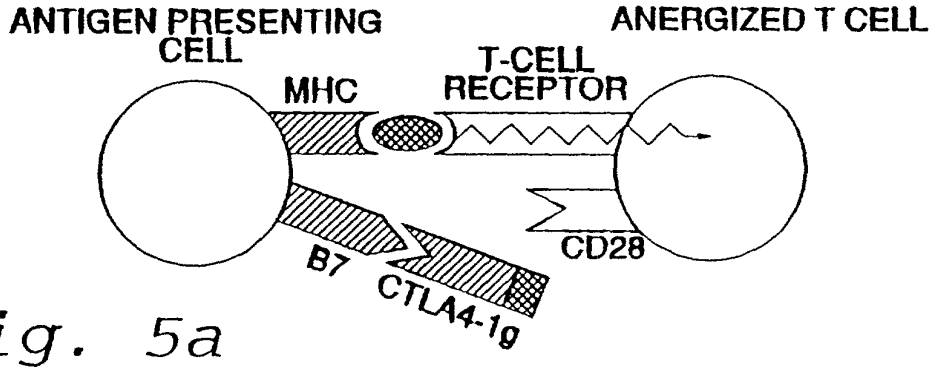


Fig. 5a

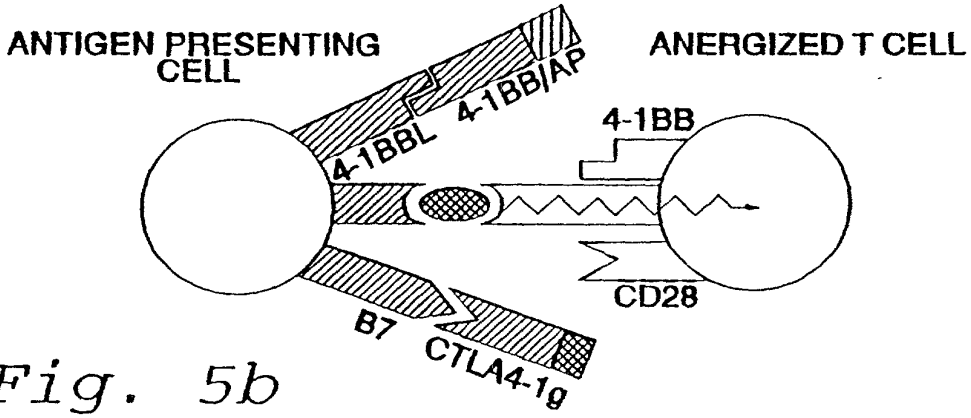


Fig. 5b

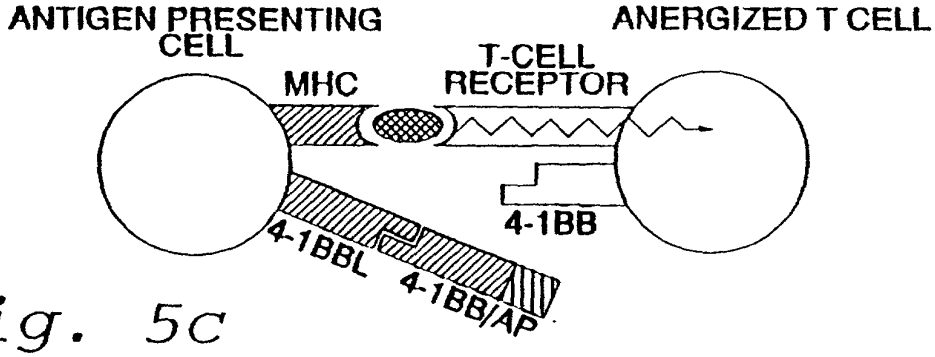


Fig. 5c